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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ADAM M. GILBERT and GARY P. STACK

Appeal 2008-5876
Application 10/663,533
Technology Center 1600

Decided: January 21, 2009

Before TONI R. SCHEINER, LORA M. GREEN, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving a claim to methods of treatment. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

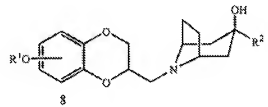
Statement of the Case

Background

"Recent studies with the selective 5-HT_{1A} antagonist WAY-100635 have confirmed a role for 5-HT_{1A} receptors in learning and memory" (Spec. 1:10-11). The Specification teaches that "post-training administration of WAY-100635 reversed the learning deficit induced by scopolamine, a cholinergic antagonist, in an autoshaping learning task" (Spec. 1:20-22).

The Claims

Claims 26 and 33-52 are on appeal. We will focus on claim 26, which is representative and reads as follows:

> 26. A method of treating a subject suffering from a condition selected from the group consisting of Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction, comprising the step of:
>
> providing to the subject suffering from said condition, a therapeutically effective amount of a compound of formula I
>
> 
>
> (I)
>
> wherein
>
> R^1 is a straight-chained alkyl of 1 to 6 carbon atoms, or a branched chain alkyl of 3 to 8 carbon atoms; and
>
> R^2 is phenyl, naphthyl, anthracyl, phenanthryl, pyridyl, pyrimidyl, triazinyl, furyl, pyrrolyl, pyrazolyl, indolyl, imidazolyl, benzofuryl, benzothienyl, oxazolyl, or thiazolyl each optionally substituted with 0 to 3 substituents selected from straight-chain alkyl of 1 to 6 carbon atoms, branched-chain alkyl of 3 to 8 carbon atoms, alkoxy of 1 to

6 carbon atoms, mono- or dialkylamino of 1 to 6 carbon atoms, nitro, halo, amino, cyano, trifluoromethyl, trifluoromethoxy and hydroxy;

or a pharmaceutically acceptable salt thereof.

The prior art

The Examiner relies on the following evidence to show unpatentability:

Barnes et al., *A review of central 5-HT receptors and their function*, 38 NEUROPHARMACOLOGY 1083-1152 (1999).

Brubacher et al., *Serotonin syndrome from venlafaxine-tranylcypromine interaction*, 38 VETERINARY HUM. TOXICOLOGY 358-61 (1996)(abstract only).

Bjorvatn et al., *Changes in sleep and wakefulness following 5-HT1A ligands given systemically and locally in different brain regions*, 9 REV. NEUROSCIENCE 265-73 (1998)(abstract only).

Ebenezer et al., *Effects of the 5-HT_{1A} Receptor Agonist 8-OH-DPAT on Operant Food Intake in Food-Deprived Pigs*, 67 PHYSIOLOGY BEHAVIOR 213-217 (1999)(abstract only).

Fletcher et al., *A pharmacological analysis of the eating response induced by 8-OH-DPAT injected into the dorsal raphe nucleus reveals the involvement of a dopaminergic mechanism*, 100 PSYCHOPHARMACOLOGY 188-94 (1990)(abstract only).

Gillin et al., *Inhibition of REM sleep by ipsapirone, a 5HT1A agonist, in normal volunteers*, 116 PSYCHOPHARMACOLOGY 433-6 (1994)(abstract only).

Kwon et al., *List of Drugs in Development for Neurodegenerative Diseases*, 1 NEURODEGENERATIVE DISEASE 113-152 (2004).

Lanfumey et al., *5-HT$_1$ Receptors*, 3 CURRENT DRUG TARGETS – CNS & NEUR. DISEASE 1-10 (2004).

Matuszewich et al., *Partial antagonism of 8-OH-DPAT's effects on male rat sexual behavior with a D2, but not a 5-HT1A, antagonist*, 820 BRAIN RESEARCH 55-62 (1999) (Abstract only).

Moreau et al., *Behavioral profile of the 5HT1A receptor antagonist (S)-UH-301 in rodents and monkeys*, 29 BRAIN RESEARCH BULLETIN 901-4 (1992) (Abstract only).

Oerther et al., *Temperature set-point changes induced by DA D2/3 and 5-HT1A receptor agonists in the rat*, 11 NEUROREPORT 3949-51 (2000) (Abstract only).

Ootsuka et al., *5-Hydroxytryptamine 1A receptors inhibit cold-induced sympathetically mediated cutaneous vasoconstriction in rabbits*, 552 J. PHYSIOLOGY 303-14 (2003).

Schechter et al., *The potential utility of 5-HT1A receptor antagonists in the treatment of cognitive dysfunction associated with Alzheimer's disease*, 8 CURRENT PHARMACEUTICAL DESIGN 139-45 (2002)(Abstract only).

Sorensen et al., *The selective 5-HT(1A) receptor antagonist p-MPPI antagonizes sleep-waking and behavioural effects of 8-OH-DPAT in rats*, 121 BEHAVIOURAL BRAIN RESEARCH 181-7 (2001)(Abstract only).

Wijngaarden et al., *Serotonin agonists and antagonists*, 112 RECL. TRAV. CHIM. PAYS-BAS 126-130 (1993).

The issue

The Examiner rejected claims 26 and 33-52 under 35 U.S.C. § 112, first paragraph as being nonenabled (Ans. 4-8).

The Examiner finds that "the nexus between Alzheimer's disease . . . and $5HT_{1A}$ receptor antagonism is not established" (Ans. 7). The Examiner

finds that the "prior art shows that there is no umbrella drug known to be effective in treating all the diseases/conditions claimed" (Ans. 7). The Examiner finds that it would require "undue experimentation in order to make and use the invention" (Ans. 8).

Appellants contend that "there is an established nexus between the antagonism at the 5-HT_{1A} receptor and treatment of the claimed conditions" (App. Br. 4). Appellants cite "references to establish the nexus between each of the listed conditions and the antagonism at the 5-HT_{1A} receptor" (App. Br. 5). Appellants further contend that "the skilled artisan would accept the disclosed model as reasonably correlating to the claimed effects and, as such, the Office must consider accept the object truth of the information unless there is evidence in the record to the contrary" (App. Br. 8).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Did the Examiner err in finding that it would require undue experimentation to treat Alzheimer's disease and other disorders using the compounds of Formula I?

Findings of Fact (FF)

Breadth of Claims

1. The Examiner finds that the "claims are broad due to the high number of compounds and diseases they embody. Formula I encompasses many different compounds due to the breadth of its variables" (Ans. 5).

Presence of Working Examples

2. The Specification teaches that "the compounds of this invention have potent affinity for and antagonist activity at brain 5-HT_{1A} serotonin receptors" (Spec. 11:9-10).

3. The Examiner finds that "[n]o working example exists showing that a claimed compound is effective at treating all the claimed diseases" (Ans. 8).

Amount of Direction or Guidance Presented

4. The Examiner finds that the "evidence fails to show that the claimed compounds are capable of treating the claimed diseases" (Ans. 8).

5. The Specification only mentions "Alzheimer's disease" once, stating that the "compounds of the invention are exceedingly interesting and useful for treating the cognitive deficits due to . . . Alzheimer's disease" (Spec. 11:10-12).

State of the Prior Art and Unpredictability of the Art

6. The only suggestion connecting 5-HT_{1A} serotonin receptor antagonist with Alzheimer's is found in Schechter, who states that "a very compelling rationale has been developed for the therapeutic potential of 5-HT1A receptor antagonists in Alzheimer's disease" (Schechter abstract). (The Lanfumey reference simply cites Schechter's work (*see* Lanfumey 5, col. 1). Schechter provides no evidence to support this position (*see* Schechter abstract).

7. Barnes teaches the unpredictability of clinical treatments with 5-HT1A antagonists, noting that "[r]ecent clinical studies have reported evidence that the therapeutic effect of antidepressant drugs can be improved

by the adjunctive treatment with pindolol . . . although this has not been confirmed in other studies" (Barnes 1091, col. 1).

8. Kwon teaches that "[n]eurodegenerative diseases are an increasingly important issue in our society. There are, however, still many obstacles on the way to finding methods for cure" (Kwon 113).

9. Kwon teaches 551 different drugs (*see* Kwon 113-151). Kwon teaches that research and development of DPP-225, a putative Alzheimer's drug that was a 5-HT antagonist, was discontinued (*see* Kwon 124, #159).

10. Kwon teaches that SB-271046, a putative Alzheimer's drug that was a 5-HT antagonist, was discontinued (Kwon 145, #464).

11. The Examiner finds that the "high degree of unpredictability is well recognized in the $5HT_{1A}$ receptor ligand art" (Ans. 6).

Quantity of Experimentation

12. The Examiner finds that the "quantity of experimentation necessary to make or use the disclosed invention is high" (Ans. 8).

13. Kwon teaches that even after identification of the drug compound and prior to clinical testing, a very large quantity of experimentation is required (*see* Kwon 152). Specifically, Kwon notes that the "Discovery" phase involves

> [l]ate research state, preparation for human testing: adaptation of research chemical synthesis (mg) to larger scale (kg), selection of salt form, selection of galenical form, design of clinical proof of concept studies, definition of endpoints, selection of biomarkers for clinical testing, additional safety testing, IND (investigational new drug) filing, clinical ethical review boards.

(Kwon 152, col. 1.)

Skill in the Art

14. The Examiner finds that the "art requires a high level of skill to perform. $5HT_{1A}$ receptors have subclasses differing in their structures, regional distribution, pharmacology, modes of actions, and functions" (Ans. 7).

Principles of Law

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

> Factors to be considered in determining whether a disclosure would require undue experimentation ... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Analysis

The Examiner concludes that a "person of ordinary skill in the art would be subjected to undue experimentation in order to make and use the invention" (Ans. 8). Based upon balancing the factors in the *Wands* analysis, we agree.

The claim is very broad, encompassing treatment of a number of different disease conditions with a large number of different chemical compounds (FF 1). *See Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 545 F.3d 1312, 1315 (Fed. Cir. 2008)("[T]he trial court opined that formula I of the alleged prior art discloses hundreds or thousands of compounds and several diseases").

While the Examiner finds a "high" skill level (FF 14), the Specification provides no working examples of any treatment of any disease with the claimed compounds (FF 2-3) and provides no guidance or teaching in the application of the compounds to diseases as diverse as Alzheimer's disease (FF 4-5).

There is evidence showing the large quantity of experimentation necessary (FF 12-13). There is also evidence demonstrating the unpredictability of 5-HT1A agonists and other compounds in treating neurological diseases such as Alzheimer's disease (FF 7-11).

While Schechter (directly and as cited by Lanfumey) speculates that 5-HT1A antagonists have therapeutic potential for Alzheimer's disease, the reference does not provide any evidence, whether in vivo, in vitro, or other experimental evidence in an Alzheimer's disease model to support this

speculation (FF 6). *See Impax,* 545 F.3d at 1315. ("[T]he language in the '940 patent discussing conditions implicating glutamate is speculative, at best").

We are not persuaded by Appellants' argument that "there is an established nexus between the antagonism at the 5-HT_{1A} receptor and treatment of the claimed conditions" (App. Br. 4). Focusing on Alzheimer's disease, other than the speculation by Schechter discussed above, there is no cited evidence linking antagonism at the 5-HT_{1A} receptor and treatment of Alzheimer's disease. There is evidence, however, from the Kwon reference, that attempts to treat Alzheimer's disease using antagonists at the 5-HT receptor were discontinued (FF 9-10).

We are not persuaded by Appellants' argument that "the skilled artisan would accept the disclosed model as reasonably correlating to the claimed effects" (App. Br. 8). While Appellants cite *Brana,* the facts of *Brana* are inapposite. In *Brana,* the evidence presented to demonstrate in vivo effectiveness was that the "specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, ***in vitro.***" *In re Brana,* 51 F.3d 1560, 1563 (Fed. Cir. 1995). Thus, *Brana* relied upon evidence of efficacy in a disease model to demonstrate enablement. *Id.* In the instant fact pattern, Appellants have not identified any model for Alzheimer's disease nor does the Specification contain any evidence of efficacy in any disease model whatsoever (FF 2-5).

Conclusions of Law

The Examiner did not err in finding that it would require undue experimentation to treat Alzheimer's disease and other disorders using the compounds of Formula I.

SUMMARY

In summary, we affirm the rejection of claim 26 under 35 U.S.C. § 112, first paragraph as being nonenabled. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 33-52 as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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